GLUCOPHAGE 500 mg, 850 mg and 1 000 mg PI

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

GLUCOPHAGE 500 mg tablet

GLUCOPHAGE 850 mg tablet

GLUCOPHAGE 1 000 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **GLUCOPHAGE 500 mg** tablet contains 500 mg metformin hydrochloride corresponding to 390 mg metformin base.

Each **GLUCOPHAGE 850 mg** tablet contains 850 mg metformin hydrochloride corresponding to 663 mg metformin base.

Each **GLUCOPHAGE 1 000 mg** tablet contains 1 000 mg metformin hydrochloride corresponding to 780 mg metformin base.

Sugar-free.

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

GLUCOPHAGE 500 mg: White, round, biconvex, film-coated tablets.

GLUCOPHAGE 850 mg: White, round, convex, film-coated tablets.

GLUCOPHAGE 1 000 mg: White, oval, biconvex, bisected, film-coated tablets with “1000” embossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of type 2 diabetes mellitus, particularly in overweight patients, when dietary management and exercise alone does not result in adequate glycaemic control.

- In adults, Glucophage film-coated tablets may be used as monotherapy or in combination with other oral antidiabetic medicines or with insulin.
- In children over 12 years of age and adolescents with type 2 diabetes mellitus, Glucophage film-coated tablets may be used as monotherapy or in combination with insulin.

A reduction of diabetic complications has been shown in overweight type 2 diabetic adult patients treated with metformin hydrochloride immediate-release as first-line therapy after diet failure.

4.2 Posology and method of administration

It is important that Glucophage tablets be taken in divided doses with meals.

Monotherapy or combination with other oral antidiabetic medicines

Adults

- Initially, one 500 mg tablet three times a day, or one 850 mg or 1 000 mg tablet twice a day, with or after meals.
- After 10 to 15 days the dose should be adjusted according to blood glucose measurements. A slow increase in dose may improve gastrointestinal tolerability.
- Good diabetic control may be achieved within a few days, but it is not unusual for the full effect to be delayed for up to two weeks. If control is incomplete a cautious increase in dosage to a maximum of 2 550 mg daily is justified. Once control has been obtained it may be possible to reduce the dosage of Glucophage.

- In patients receiving a high metformin dose (2000 to 3000 mg per day), it is possible to replace two Glucophage 500 mg film-coated tablets with one Glucophage 1000 mg film-coated tablet.
- The maximum recommended dose of Glucophage is 3000 mg daily, taken as 3 divided doses.
- If transfer from another oral antidiabetic medicine is intended, discontinue the other medicine and initiate metformin at the dose indicated above.

Combination with insulin

Glucophage and insulin may be used in combination therapy to achieve better blood glucose control. Glucophage is given at the usual starting dose of 500 mg or 850 mg 2 or 3 times daily, while insulin dosage is adjusted on the basis of blood glucose measurements.

Paediatric patients

Glucophage can be used in children from 12 years of age and adolescents as monotherapy or in combination with insulin.

- The usual starting dose is 500 mg or 850 mg once daily, given during meals or after meals.
- After 10 to 15 days the dose should be adjusted on the basis of blood glucose measurements. A slow increase of dose may improve gastrointestinal tolerability.
- The maximum recommended dose of Glucophage is 2 000 mg daily, taken as 2 or 3 divided doses.

Patients with renal impairment

A GFR should be assessed before initiation of treatment with metformin containing products and at least annually thereafter. In patients at an increased risk of further

progression of renal impairment and in the elderly, renal function should be assessed more frequently, e.g. every 3-6 months.

Glucophage may be used in patients with moderate renal impairment stage 3 (creatinine clearance [CrCl] between 30 and 59 mL/min or estimated glomerular filtration rate [eGFR] between 30 – 59 ml/min/1.73m^2) only in the absence of other conditions that may increase the risk of lactic acidosis (see section 4.4) and with the following dose adjustments:
The starting dose is 500 mg or 850 mg Glucophage. The maximum daily dose is 1000 mg.

The renal function should be closely monitored:

- Every 3-6 months in patients with CrCl between 45 and 59 mL/min or eGFR between 45 and 59 mL/min/1.73m^2.
- Every 3 months in patients with CrCl between 30 and 44 mL/min or eGFR between 30 and 44 mL/min/1.73m^2.

If CrCl or eGFR fall below 30 mL/min or 30 mL/min/1.73m^2 respectively, Glucophage must be discontinued immediately.

GFR (mL/min)	Total maximum daily dose (to be divided into 2-3 daily doses)	Additional considerations
60-89	3000 mg	Dose reduction may be considered in relation to declining renal function.
45 – 59	2000 mg	Factors that may increase the risk of lactic acidosis (see section 4.4) should be reviewed before considering initiation of metformin. The starting dose is at most half of the maximum dose.
30 - 44	1000 mg	
<30	-	Metformin is contraindicated

Elderly

Due to the potential for decreased renal function in elderly subjects, it is recommended that the Glucophage dose be adjusted based on renal function. Regular assessment of renal function is necessary.

Benefit in the reduction of risk or delay of the onset of type 2 diabetes mellitus has not been established in patients 75 years and older (see section 5.1) Glucophage initiation is therefore not recommended in these patients (see section 4.4).

4.3 Contraindications

- Hypersensitivity to metformin hydrochloride or to any of the excipients listed in section 6.1.
- Any type of acute metabolic acidosis (such as lactic acidosis, diabetic ketoacidosis)
- Diabetic pre-coma.
- Disease (especially acute disease, or worsening of chronic disease) which may cause tissue hypoxia, such as unstable congestive heart failure, respiratory failure, recent myocardial infarction or shock.
- Severe renal failure (CrCl below 30 mL/min or eGFR below 30 mL/min/1.73m^2).
- Acute conditions with the potential to alter renal function such as dehydration, severe infection or shock.

- Hepatic insufficiency, acute alcohol intoxication, alcoholism

4.4 Special warnings and precautions for use

Lactic acidosis

Lactic acidosis is a very rare, but serious (high mortality in the absence of prompt treatment), metabolic complication.

Risk factors include poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, severe infection, hepatic insufficiency, and any condition associated with hypoxia (such as decompensated cardiac failure, acute myocardial infarction) or the concomitant use of medications which might cause lactic acidosis (such as NRTIs), (see also section 5).

Lactic acidosis can occur due to metformin accumulation.

Reported cases of lactic acidosis in patients on Glucophage have occurred primarily in diabetic patients with acute renal failure or acute worsening of renal function.

Special caution should therefore be paid to situations where renal function may become acutely impaired, for example in case of dehydration (severe or prolonged diarrhoea or vomiting) or when initiating medications which can acutely impair renal function (such as antihypertensives, diuretics and NSAIDs).

In the acute conditions listed, Glucophage must be immediately and temporarily discontinued.

The following non-specific symptoms could be signs of lactic acidosis: such as muscle cramps, digestive disorders as abdominal pain and asthenia.

Diagnosis

Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH (below 7.35), plasma lactate levels above 5 mmol/l, and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, Glucophage should be discontinued and the patient should be hospitalised **immediately.**

Medical practitioners must alert the patients on the risk and on the symptoms of lactic acidosis.

Patients should be instructed to immediately seek medical attention and to stop taking Glucophage.

Glucophage must be immediately discontinued, at least temporarily, until the situation is clarified. Reintroduction of Glucophage should then be discussed taking into account the benefit/risk ratio on an individual basis as well as renal function.

Renal function

As Glucophage is excreted by kidney, it is recommended that CrCl (this can be estimated from creatinine levels by using Cockcroft-Gault formula) or cGFR should be determined before initiating treatment and regularly thereafter:

- At least annually in patients with normal renal function,
- At least every 3 to 6 months in patients with CrCl between 45 and 59 mL/min or eGFR between 45 and 59 mL/min/1.73m^2 and in elderly subjects.
- At least every 3 months in patients with CrCl between 30 and 44 mL/min or eGFR between 30 and 44 mL/min/1.73m^2.

In case CrCl is below 30 mL/min or eGFR is below 30 mL/min/1.73m^2 respectively, Glucophage is contraindicated (see section 4.3).

Decreased renal function in elderly subjects is frequent and asymptomatic.

Special caution should be exercised in situations where renal function may become acutely impaired, for example due to dehydration (severe or prolonged diarrhoea or

vomiting), or when initiating medicines which can acutely impair renal function (such as antihypertensive therapy or diuretic therapy and when starting therapy with a NSAID).
In the acute conditions listed, Glucophage must be immediately and temporarily discontinued.
In these cases, it is also recommended to check renal function before initiating treatment with Glucophage.

Cardiac function

Patients with heart failure are more at risk of hypoxia and renal insufficiency. In patients with stable chronic heart failure, Glucophage may be used with a regular monitoring of cardiac and renal function.
For patients with acute and unstable heart failure, Glucophage is contraindicated.

Administration of iodinated contrast medicines

Intravascular administration of iodinated contrast medicines may lead to contrast induced nephropathy, resulting in metformin accumulation and an increased risk of lactic acidosis. Glucophage should be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections 4.2 and 4.5.

Surgery

Glucophage must be discontinued 48 hours prior to elective major surgical interventions and may not be reinstated until 48 hours afterwards or resumption or oral nutrition, and only after renal function has been re-evaluated and has not deteriorated further.

Paediatric patients

The diagnosis of type 2 diabetes mellitus must be confirmed before treatment with Glucophage is initiated.

No effect of Glucophage on growth and puberty has been detected during controlled clinical studies of one-year duration but no long-term data on these specific points are available. Therefore, a careful follow-up of the effect of Glucophage on these parameters in Glucophage treated children, especially pre-pubescent children, is recommended.

Other precautions:

- All patients should continue their diet with a regular distribution of carbohydrate intake during the day. Overweight patients should continue their energy-restricted diet.
- The usual laboratory tests for diabetes monitoring should be performed regularly.
- Glucophage alone never causes hypoglycaemia, although caution is advised when it is used in combination with insulin, ~~or~~ sulfonylureas or meglitinides.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use not recommended

Alcohol

The risk of lactic acidosis is increased in acute alcohol intoxication, particularly in case of fasting or malnutrition or hepatic insufficiency.

It is recommended that consumption of alcohol and alcohol-containing medicines be avoided.

Iodinated contrast medicines

Glucophage must be discontinued prior to or at the time of the imaging procedure and not restarted until at least 48 hours after, provided that renal function has been re-evaluated and found to be stable, see sections 4.2 and 4.4

Practitioners prescribing metformin should be aware that patients receiving certain

antiretroviral medication e.g. protease inhibitors may be independently more prone to develop lactic acidosis.

Combinations to be used with caution

Medicinal products with intrinsic hyperglycaemic activity (e.g. glucocorticoids and tetracosactides, beta-2-agonists, danazol, and chlorpromazine at high dosages of 100 mg per day, diuretics): More frequent blood glucose monitoring may be required, especially at the beginning of treatment. If necessary, adjust the metformin dosage during therapy with the respective medicinal product and upon its discontinuation.

Diuretics, especially loop diuretics, may increase the risk of lactic acidosis due to their potential to decrease renal function. When starting or frequently using such products in combination with metformin, close monitoring of renal function is necessary.

Organic cation transporters (OCT)

Metformin is a substrate of both transporters OCT1 and OCT2.

Co-administration of metformin with

- Substrates/inhibitors of OCT1 (such as verapamil) may reduce efficacy of metformin.
- Inducers of OCT1 (such as rifampicin) may increase gastrointestinal absorption and efficacy of metformin.
- Substrates/inhibitors of OCT2 (such as cimetidine, dolutegravir, ranolazine, trimethoprime, vandetanib, isavuconazole) may decrease the renal elimination of metformin and thus lead to an increase metformin plasma concentration.
- Inhibitors of both OCT1 and OCT2 (such as crizotinib, olaparib) may alter efficacy and renal elimination of metformin.

Therefore, caution is advised when these drugs are co-administered with metformin and a dose adjustment may be considered, particularly in patients with renal impairment.

4.6 Fertility, pregnancy and lactation

Pregnancy

Uncontrolled diabetes during pregnancy (gestational or permanent) is associated with increased congenital abnormalities and perinatal mortality.

A limited amount of data from the use of Glucophage in pregnant women does not indicate an increased risk of congenital abnormalities.

Safety in pregnancy and lactation has not been established in humans. However, animal studies do not indicate harmful effects with respect to pregnancy, embryonal or foetal development, parturition or postnatal development.

When the patient plans to become pregnant and during pregnancy, diabetes should not be treated with Glucophage but insulin should be used to maintain blood glucose levels as close to normal as possible in order to lower the risk of foetal malformations associated with abnormal blood glucose levels.

Lactation

Glucophage is excreted into milk in lactating rats.

Glucophage is excreted into human breast milk in very small amounts. No adverse effects were observed in breastfed newborns/infants. However, as only limited data are available, breast-feeding is not recommended during Glucophage treatment.

A decision on whether to discontinue breast-feeding or to discontinue Glucophage needs to take into account the benefit of breast-feeding, the importance of the medicinal product to the mother, and the potential risk of adverse effects in the infant.

Fertility

Fertility of male and female rats was unaffected by Glucophage when administered at

doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

4.7 Effects on ability to drive and use machinery

Glucophage monotherapy does not cause hypoglycaemia and therefore has no effect on the ability to drive or to use machines.

However, patients should be alerted to the risk of hypoglycaemia when Glucophage is used in combination with other antidiabetic medicines (e.g. sulfonylureas, insulins or meglitinides).

4.8 Undesirable effects

During treatment initiation, the most common adverse reactions are nausea, vomiting, diarrhoea, abdominal pain and loss of appetite which resolve spontaneously in most cases. To prevent them, it is recommended to take Glucophage in 2 or 3 daily doses and to increase slowly the doses.

Adverse reactions reported are listed below by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1000, < 1/100), rare (< 1/10 000), very rare (< 1/10 000) and frequency not known: cannot be estimated from the available data.

Metabolism and nutrition disorders

Very rare

- Decrease of vitamin B12 and folic acid absorption with decrease of serum levels during long-term use of Glucophage. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.
- Lactic acidosis.

Nervous system disorders

Common

- Taste disturbance.

Gastrointestinal disorders

Very common

- Gastrointestinal disorders such as nausea & vomiting, diarrhoea, abdominal pain and loss of appetite. These undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that Glucophage be taken in 2 or 3 daily doses during or after meals. A slow increase of the dose may also improve gastrointestinal tolerability.

Hepatobiliary disorders

Very rare

- Isolated reports of liver function tests abnormalities or hepatitis resolving upon metformin discontinuation.

Skin and subcutaneous tissue disorder

Very rare

- Skin reactions such as erythema, pruritus, urticaria.

Children and adolescents

In published and post marketing data and in controlled clinical studies in a limited paediatric population aged 10 - 16 years during 1year, adverse event reporting was similar in nature and severity to that reported in adults.

4.9 Overdose

Hypoglycaemia has not been seen with metformin doses of up to 85 g, although lactic

acidosis has occurred in such circumstances. In excessive dosage, and particularly if there is a possibility of accumulation, lactic acidosis may develop. Lactic acidosis is a medical emergency and must be treated in hospital. The most effective method to remove lactate and Glucophage is haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacological classification: A 21.2 Oral hypoglycaemics.

Pharmacodynamic properties

Mechanism of action

Metformin is a biguanide with anti-hyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemia.

Metformin may act via 3 mechanisms

1. Reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis.
2. In muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation.
3. Delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase.

Metformin increases the transport capacity of all types of membrane glucose transporters (GLUTs) known to date.

5.2 Pharmacokinetic Properties

Absorption

After an oral dose of metformin, Tmax is reached in 2,5 hours. Absolute bioavailability of a 500 or 850 mg metformin tablet is approximately 50 - 60 % in healthy subjects.

After an oral dose, the non-absorbed fraction recovered in faeces was 20 - 30 %.

After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear.

At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24 to 48 hours and are generally less than 1 µg/ml. In controlled clinical trials, maximum metformin plasma levels (Cmax) did not exceed 5 µg/ml, even at maximum doses.

Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40 % lower plasma peak concentration, a 25 % decrease in AUC (area under the curve) and a 35 minute prolongation of time to peak plasma concentration were observed. The clinical relevance of these decreases is unknown.

Distribution

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean Volume of Distribution ranged between 63 - 276 l.

Metabolism

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans.

Elimination

Renal clearance of metformin is > 400 ml/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6,5 hours.

When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of

metformin in plasma.

Paediatrics

Single dose study: After single doses of metformin 500 mg paediatric patients have shown similar pharmacokinetic profile to that observed in healthy adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The inactive ingredients are povidone and magnesium stearate. In addition, Glucophage 500 and 850 mg contains hydroxypropylmethylcellulose and Glucophage 1 000 mg contains opadry clear.

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

Keep out of reach of children.

The blister should not be removed from the carton until required for use.

6.5 Nature and contents of container

Glucophage 500 mg: 90’s in transparent/colourless PVC/aluminium blisters.

Glucophage 850 mg: 60’s in transparent/colourless PVC/aluminium blisters.

Glucophage 1 000 mg: 60’s in transparent/colourless PVC/aluminium blisters.

6.6 Special precautions for disposal

No special requirements

7. HOLDER OF CERTIFICATE FOR REGISTRATION

Merck (Pty) Ltd

1 Friesland Drive

Longmeadow Business Estate South

Modderfontein, 1645

South Africa

8. REGISTRATION NUMBERS

Glucophage 500 mg: G3244 (Act 101/1965)

Glucophage 850 mg: F/21.2/145

Glucophage 1 000 mg: 37/21.2/0272

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 November 2021